NR

09/763129

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

15

Applicant's or agent's file reference 001009330WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US99/16724	International filing date *(day/month/year)* 19 AUGUST 1999	Priority date *(day/month/year)* 19 AUGUST 1998
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant AJINOMOTO CO., INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17 MARCH 2000	10 OCTOBER 2000
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer PHILLIP GAMBEL
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

Form PCT/IPEA/409 (cover sheet) (July 1998)★

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/16724

I. Basis of th report

1. With regard to the elements of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-20 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of

[X] the claims:
pages 21-23 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of

[X] the drawings:
pages 1-5 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of

[X] the sequence listing part of the description:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[ ] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

5. [X] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/16724

V. Reasoned statement und r Article 35(2) with regard to novelty, inventive step r industrial applicability; citations and explanations supp rting such statement

1. statement

Novelty (N)	Claims	1-21	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-21	NO
Industrial Applicability (IA)	Claims	1-21	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1-21 lack an inventive step under PCT Article 33(3) as being obvious over Yamamoto et al. (Blood. 1996, Vol. 88, page 677, Abstract 172A) and/or Kageyama et al. (Br. J. Pharmacol. 1997, Vol. 122, pages 165-171) and/or Poletti et al. (J. Vasc. Surg. 1997, Vol. 26, pages 366-372) in view of the art known methods at the time the invention was made to generate humanized antibodies to antigens of interest, as acknowledged on pages 3-13 of the Description.

Yamamoto teach that the anti-von Willebrand factor antibody AJvW-2 inhibit arterial thrombosis (See Abstract).

Kageyama et al. teach that the anti-von Willebrand factor antibody AJvW-2 inhibited a number of thrombotic effects and bleeding risks (see entire document, including the Abstract).

Poletti et al. teach the prevention of arterial thrombosis with the anti-von Willebrand factor antibody AJvW-2 inhibit arterial thrombosis (see entire document, including the Abstract).

Yamamoto, Kageyama et al., Poletti et al. differ from the claimed inventions by not humanizing the anti-von Willebrand factor antibody AJvW-2 and using the humanized AJvW-2 antibodies in the treatment of patients.

It was well known at the time the invention was made to generate humanized antibodies to antigens of interest, as acknowledged on pages 3-13 of the Description, for antibodies to be used as diagnostic and therapeutic tools in humans. Such humanized antibodies would have longer half -life, have human antibody effector functions if desired and have decreased immunogenicity as compared to their non-human (e.g. murine) counterparts.

Given the art known methods to generate humanized antibodies for various purposes, including detection, diagnostic and therapeutic modalities; the ordinary artisan would have been motivated to humanize the von Willebrand factor / AJvW-2 specific antibody of the prior art for such purposes with an expectation of success at the time the invention was made. Although the references are silent about the exact sequences of the AJvW-2 specific antibody, the recombinant techniques and computer analyses of CDR grafting as known and practiced at the time the (Continued on Supplemental Sheet.)

Supplemental Box
(To be used when the spac in any f the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(7): A61K 39/395; C07K 16/18, 16/36; C12N 5/12 and US Cl.: 424/130.1, 133.1, 141.1, 145.1, 158.1; 435/70.21, 326, 328, 332, 337, 343, 346; 530/387.1, 387.3, 388.1, 388.2, 388.25, 388.7

I. BASIS OF REPORT:

5. (Some) amendments are considered to go beyond the disclosure as filed:
NONE

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
invention was made would have resulted in the same or very nearly the same structural and functional characteristics of the instant claims since both the reference and instant invention use the same techniques, the same antibody specificities and the same goals. The claimed functional limitations encompassed by the claims would be expected properties for selecting AJvW-2 specific antibodies to specifically bind von Willebrand factor and to detect von Willebrand factor or to inhibit thrombotic events and interactions. The claims drawn to specifically defined AJvW-2 antibody competitors were obvious over the prior art teachings of the same AJvW-2 specific antibodies and hybridomas cell lines, since the record does not contain any evidence that the cell lines differ in any significant manner or produce monoclonal antibodies that differ in any significant aspect from hybrid cell lines that one of ordinary skill in the art would have expected to generate using the AJvW-2 specific antibody and hybridoma as the starting material in the basic method of generating antibodies and humanizing said antibodies. There appears no evidence that the use of various sources of framework amino acids would differ in an unexpected or distinct manner from those available to the ordinary artisan at the time the invention was made. Given the ability of the AJvW-2 antibody to inhibit various aspects of thrombotic conditions in experimental models, it would have been obvious to apply the humanized version of this antibody in the treatment of thrombotic conditions in humans.

One of ordinary skill in the art at time the invention was made would have been motivated to select AJvW-2-specific antibodies in diagnostic and therapeutic regimens involved with various inflammatory conditions, including treating thrombotic conditions, which rely upon von Willebrand factor. From the teachings of the references, it was apparent that one of ordinary skill in the art have had a reasonable expectation of success in producing the claimed inventions. Therefore, the inventions as a whole were prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

———— NEW CITATIONS ————
NONE

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
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CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

WO 00/10601
PCT/US99/16724

PATENT COOPERATION TREATY

09/763129

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
OBLON, Norman, F.
Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
4th floor
1755 Jefferson Davis Highway
Crystal Square Five
Arlington, VA 22202
ÉTATS-UNIS D'AMÉRIQUE

Date of mailing (day/month/year) 02 March 2000 (02.03.00)	
Applicant's or agent's file reference 001009330WO	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/US99/16724	19 August 1999 (19.08.99)	19 August 1998 (19.08.98)

Applicant
AJINOMOTO CO., INC. et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,CN,EP,IL,JP,KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CR,CU,CZ,DE,DK,DM,EA,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   02 March 2000 (02.03.00) under No. WO 00/10601

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

PCT/US99/16724

09/763129

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

OBLON, Norman, F.
Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
4th floor
1755 Jefferson Davis Highway
Crystal Square Five
Arlington, VA 22202
ÉTATS-UNIS D'AMÉRIQUE

Date of mailing (day/month/year) 21 January 2000 (21.01.00)	
Applicant's or agent's file reference 001009330WO 0010-0933-0WO	**IMPORTANT NOTIFICATION**
International application No. PCT/US99/16724	International filing date (day/month/year) 19 August 1999 (19.08.99)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 19 August 1998 (19.08.98)
Applicant AJINOMOTO CO., INC. et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
19 Augu 1998 (19.08.98)	09/136,315	US	18 Janu 2000 (18.01.00)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
Ellen Moyse

Telephone No. (41-22) 338.83.38

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/16724

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :A61K 39/395; C07K 16/18, 16/36; C12N 5/12
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/130.1, 133.1, 141.1, 145.1, 158.1; 435/70.21, 326, 328, 332, 337, 343, 346; 530/387.1, 387.3, 388.1, 388.2, 388.25, 388.7

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DIALOG, BIOSIS, CA, EMBASE, MEDLINE, USPAT
search terms: von willebrand factor, antibod?, ajvw-2

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	YAMAMOTO et al., Anti-Von Willebrand Factor Antibody AJvW-2 Specifically Inhibits Arterial but Not Venous Thrombosis in the Hamster. Blood. 1996, Volume 88, Supplemental 10, 1 Part 1-2, page 677, Abstract 172A, see entire abstract.	1-21
Y	KAGEYAMA et al. Anti-Thrombotic Effects and Bleeding Risk of AJvW-2, a Monoclonal Antibody Against Human Von Willebrand Factor. British Journal of Pharmacology. 1997, Volume 122, pages 165-171, see entire document.	1-21
Y	POLETTI et al. Prevention of Arterial Thrombosis Using a Novel Heparin with Enhanced Antiplatelet Activity and Reduced Anticoagulant Activity. 1997, Volume 26, pages 366-372, see entire document.	1-21

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
12 DECEMBER 1999

Date of mailing of the international search report
20 JAN 2000

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer
PHILLIP GAMBEL
Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)★

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/16724

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

424/130.1, 133.1, 141.1, 145.1, 158.1; 435/70.21, 326, 328, 332, 337, 343, 346; 530/387.1, 387.3, 388.1, 388.2, 388.25, 388.7

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 08 May 2000 (08.05.00)	
International application No. PCT/US99/16724	**Applicant's or agent's file reference** 001009330WO
International filing date (day/month/year) 19 August 1999 (19.08.99)	**Priority date** (day/month/year) 19 August 1998 (19.08.98)
Applicant CO, Man, Sung et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

17 March 2000 (17.03.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer R. E. Stoffel
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

European Patent Office

SUPPLEMENTARY PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 99 94 3621

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Y	EP 0 795 608 A (AJINOMOTO KK) 17 September 1997 (1997-09-17) * column 11, line 19 - column 11, line 43; claims 1-14 * ---	1-21	A61K39/395 C07K16/18 C07K16/36 C12N5/12
Y	JOLLIFFE L K: "HUMANIZED ANTIBODIES: ENHANCING THERAPEUTIC UTILITY THROUGH ANTIBODY ENGINEERING" INTERNATIONAL REVIEWS OF IMMUNOLOGY, HARWOOD ACADEMIC PUBLISHERS, LONDON, GB, vol. 10, no. 2/3, 1993, pages 241-250, XP000561185 ISSN: 0883-0185 * the whole document * -----	1-21	

TECHNICAL FIELDS SEARCHED (Int.Cl.7)

C07K

The supplementary search report has been based on the last set of claims valid and available at the start of the search.

INCOMPLETE SEARCH

The Search Division considers that the present application, or some or all of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for the following claims:

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
MUNICH	18 September 2002	Renggli, J

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C20)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 99 94 3621

This annex lists the patent family membersrelating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

18-09-2002

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0795608 A	17-09-1997	EP 0795608 A1	17-09-1997
		FI 972279 A	29-07-1997
		NO 972253 A	29-07-1997
		US 5916805 A	29-06-1999
		CA 2206423 A1	06-06-1996
		CN 1174575 A	25-02-1998
		WO 9617078 A1	06-06-1996
		US 6280731 B1	28-08-2001
		US 2002028204 A1	07-03-2002

Although claims 18-21 are directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.

Claim(s) searched completely:
1-21

Claim(s) searched incompletely:
-

Claim(s) not searched:
22

Reason for the limitation of the search:

1) Claim number 21 is present twice in the application as originally filed. The second claim is referred to as Claim 22 in the present Search Report.

2) Claim 22 is directed to a cell line producing a human immunoglobulin which competes with mouse antibody AJvW-2 for specific binding to von Willebrand factor.

It is noted that the application as a whole pertains to the production of humanized antibodies and not to human antibodies. There is no technical teaching in the application which would enable the production of a human antibody having the said property. It is moreover acknowledged in the description, page 2 that "In general, producing human immunoglobulins reactive with von Willebrand factor with high affinity (i.e. competing with the high affinity antibody AJvW-2) would be extremely difficult using typical human monoclonal antibody production techniques". It is finally noted that the present application does not disclose any alternative techniques which would facilitate the development of said human antibody.

Thus, the subject-matter of claim 22 of the present application is neither technically supported nor sufficiently disclosed contrary to the requirements of Articles 84 and 83 EPC.

The defect is such that no search has been carried out for the subject-matter of claim 22.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: NORMAN F. OBLON
OBLON, SPIVAK, MCCLELLAN, MAIER & NEUSTADT, P.C.
CRYSTAL SQUARE FIVE, FOURTH FLOOR
1755 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202

PCT COPY

WRITTEN OPINION

(PCT Rule 66)

Reply due 8-5-00

Date of Mailing *(day/month/year)*	05 JUN 2000
Applicant's or agent's file reference: 0010-0933-0WO	REPLY DUE: within TWO months from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/16724	19 AUGUST 1999	19 AUGUST 1998

International Patent Classification (IPC) or both national classification and IPC
Please See Supplemental Sheet.

I.D.S. COPY

Applicant
AJINOMOTO CO., INC.

DOCKET NO. 0010-0933-0

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	[X]	Basis of the opinion
II	[ ]	Priority
III	[ ]	Non-establishment of opinion with regard to novelty, inventive step or industrial applicability
IV	[ ]	Lack of unity of invention
V	[X]	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[ ]	Certain documents cited
VII	[ ]	Certain defects in the international application
VIII	[ ]	Certain observations on the international application

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JUN 07 2000
OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C.

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension., see Rule 66.2(d).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 *bis*.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 19 DECEMBER 2000.

Name and mailing address of the IPEA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	PHILLIP GAMBEL
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

WRITTEN OPINION

International application No.
PCT/US99/16724

I. Basis of the opinion

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:
pages 1-20, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

☒ the claims:
pages 21-23, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

☒ the drawings:
pages 1-5, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

☒ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages NONE

☒ the claims, Nos. NONE

☒ the drawings, sheets/~~fig~~ NONE

5. ☐ This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*

WRITTEN OPINION

International application No.
PCT/US99/16724

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	1-21	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-21	NO
Industrial Applicability (IA)	Claims	1-21	YES
	Claims	NONE	NO

2. citations and explanations

Claims 1-21 lack an inventive step under PCT Article 33(3) as being obvious over Yamamoto et al. (Blood. 1996, Vol. 88, page 677, Abstract 172A) and/or Kageyama et al. (Br. J. Pharmacol. 1997, Vol. 122, pages 165-171) and/or Poletti et al. (J. Vasc. Surg. 1997, Vol. 26, pages 366-372) in view of the art known methods at the time the invention was made to generate humanized antibodies to antigens of interest, as acknowledged on pages 3-13 of the Description.

Yamamoto teach that the anti-von Willebrand factor antibody AJvW-2 inhibit arterial thrombosis (See Abstract).

Kageyama et al. teach that the anti-von Willebrand factor antibody AJvW-2 inhibited a number of thrombotic effects and bleeding risks (see entire document, including the Abstract).

Poletti et al. teach the prevention of arterial thrombosis with the anti-von Willebrand factor antibody AJvW-2 inhibit arterial thrombosis (see entire document, including the Abstract).

Yamamoto, Kageyama et al., Poletti et al. differ from the claimed inventions by not humanizing the anti-von Willebrand factor antibody AJvW-2 and using the humanized AJvW-2 antibodies in the treatment of patients.

It was well known at the time the invention was made to generate humanized antibodies to antigens of interest, as acknowledged on pages 3-13 of the Description, for antibodies to be used as diagnostic and therapeutic tools in humans. Such humanized antibodies would have longer half -life, have human antibody effector functions if desired and have decreased immunogenicity as compared to their non-human (e.g. murine) counterparts.

Given the art known methods to generate humanized antibodies for various purposes, including detection, diagnostic and therapeutic modalities; the ordinary artisan would have been motivated to humanize the von Willebrand factor / AJvW-2 specific antibody of the prior art for such purposes with an expectation of success at the time the invention was made. Although the references are silent about the exact sequences of the AJvW-2 specific antibody, the recombinant techniques and computer analyses of CDR grafting as known and practiced at the time the (Continued on Supplemental Sheet.)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

TIME LIMIT:

The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(7): A61K 39/395; C07K 16/18, 16/36; C12N 5/12 and US Cl.: 424/130.1, 133.1, 141.1, 145.1, 158.1; 435/70.21, 326, 328, 332, 337, 343, 346; 530/387.1, 387.3, 388.1, 388.2, 388.25, 388.7

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
invention was made would have resulted in the same or very nearly the same structural and functional characteristics of the instant claims since both the reference and instant invention use the same techniques, the same antibody specificities and the same goals. The claimed functional limitations encompassed by the claims would be expected properties for selecting AJvW-2 specific antibodies to specifically bind von Willebrand factor and to detect von Willebrand factor or to inhibit thrombotic events and interactions. The claims drawn to specifically defined AJvW-2 antibody competitors were obvious over the prior art teachings of the same AJvW-2 specific antibodies and hybridomas cell lines, since the record does not contain any evidence that the cell lines differ in any significant manner or produce monoclonal antibodies that differ in any significant aspect from hybrid cell lines that one of ordinary skill in the art would have expected to generate using the AJvW-2 specific antibody and hybridoma as the starting material in the basic method of generating antibodies and humanizing said antibodies. There appears no evidence that the use of various sources of framework amino acids would differ in an unexpected or distinct manner from those available to the ordinary artisan at the time the invention was made. Given the ability of the AJvW-2 antibody to inhibit various aspects of thrombotic conditions in experimental models, it would have been obvious to apply the humanized version of this antibody in the treatment of thrombotic conditions in humans.

One of ordinary skill in the art at time the invention was made would have been motivated to select AJvW-2-specific antibodies in diagnostic and therapeutic regimens involved with various inflammatory conditions, including treating thrombotic conditions, which rely upon von Willebrand factor. From the teachings of the references, it was apparent that one of ordinary skill in the art have had a reasonable expectation of success in producing the claimed inventions. Therefore, the inventions as a whole were prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

---------- NEW CITATIONS ----------
NONE